



Computer simulations of phospholipid - membrane thermodynamic fluctuations

Pedersen, U.R.; Peters, Günther H.j.; Schröder, T.B.; Dyre, J.C.

Published in:
Arxiv.org: Physics

Publication date:
2008

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
Pedersen, U. R., Peters, G. H. J., Schröder, T. B., & Dyre, J. C. (2008). Computer simulations of phospholipid - membrane thermodynamic fluctuations. *Arxiv.org: Physics*, *arXiv:0811.3317v1*.

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Computer simulations of phospholipid-membrane thermodynamic fluctuations

Ulf R. Pedersen* (urp@ruc.dk), Günther H. Peters†,
Thomas B. Schrøder* and Jeppe C. Dyre*

*DNRF Centre “Glass and Time,” IMFUFA, Department of Sciences,
Roskilde University, Postbox 260, DK-4000 Roskilde, Denmark.

†Center for Membrane Biophysics (MEMPHYS), Department of Chemistry,
Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

January 27, 2014

Abstract

This paper reports all-atom computer simulations of five phospholipid membranes, DMPC, DPPC, DMPG, DMPS, and DMPSH, with a focus on the thermal equilibrium fluctuations of volume, energy, area, thickness, and order parameter. For the slow fluctuations at constant temperature and pressure (defined by averaging over 0.5 nanosecond) volume and energy exhibit strong correlation. These quantities on the other hand do not correlate significantly with area, thickness, or order parameter. The correlations are mainly reported for the fluid phase, but we also give results for the ordered (gel) phase of two membranes, showing a similar picture. The cause of the observed strong correlations is identified by splitting volume and energy into contributions from tails, heads, and water, showing that the slow volume-energy fluctuations derive from the tail region’s van der Waals interactions and are thus analogous the similar strong correlations recently observed in computer simulations of the Lennard-Jones and other simple van der Waals type liquids. The strong correlations reported here confirm an assumption of a recent theory for nerve signal propagation proposed by Heimburg and Jackson (2005).

In 2005 Heimburg and Jackson showed that biomembranes may carry solitonic sound waves with a maximum amplitude and a minimum velocity of the solitons that is close to the propagation velocity in myelinated nerves [1]. Their paper concluded: “It would be surprising if nature did not exploit these features.” Subsequent works by the same authors argue directly that nerve signals are not primarily electrical, but solitonic sound waves carried by the nerve cell membrane [2]. The conventional wisdom is that nerve signals propagate via electrical current as formulated in the Hodgkin-Huxley theory [3]. The

Heimburg-Jackson theory, which is obviously controversial, explains anaesthesia as a straightforward effect of melting-point depression of the order-disorder transition that biomembranes (for otherwise biologically unknown reasons) have at temperatures close to physiological temperatures [4].

The Heimburg-Jackson nerve-signal theory motivated this study. An element of the theory is the assumption that volume and enthalpy correlate strongly in their thermal equilibrium fluctuations, at least as regards the slow parts of these fluctuations. This assumption was justified by observations that membrane specific heat and compressibility are proportional in their temperature dependence, even across the phase transition [5, 6]. Such a postulated strong correlation between thermodynamic variables of microstates is quite unusual in the statistical mechanical literature. Below we present first results from extensive computer simulations of different phospholipid membranes performed in order to investigate whether strong volume-energy correlations are observed and – if they are – what causes them.

Recently we studied equilibrium thermodynamic fluctuations of much simpler systems, namely various model liquids like the standard Lennard-Jones (LJ) liquid and similar systems [7, 8, 9, 10]. In many such simple liquids one finds a strong correlation between equilibrium fluctuations of the virial W and the potential energy U , when fluctuations are studied at constant particle number N , constant volume V , and constant temperature T (the so-called NVT ensemble [11]). Recall [12] that the virial $W = W(t)$ gives the non-ideal contribution to the instantaneous pressure $p = p(t)$ via the defining equation: $p(t)V = (2/3)Nk_B T(t) + W(t)$ where $T(t)$ is the instantaneous temperature defined via the instantaneous kinetic energy. The virial determines the part of the pressure that comes from interactions, i.e., in addition to the ideal gas contribution; the virial is a function of the particle positions [12]. For the LJ liquid, as well as for a united-atom toluene model, a dumbbell model, the Kob-Andersen binary LJ liquid [13], and other liquids, W and U correlate better than 90% in their equilibrium fluctuations. This reflects an effective inverse power-law potential dominating fluctuations, as detailed in Refs. [9, 10]. Liquids with poor $W - U$ correlation include water and methanol [8]. In these cases the correlations are ruined by the hydrogen bonds that are conventionally modelled via Coulomb forces – the existence of competing interactions prevents strong $W - U$ correlation in hydrogen-bonded liquids.

For liquids with time-scale separation like highly viscous liquids, strong $W - U$ correlations are particularly significant. Thus it has been shown [7, 14] that viscous liquids with strong $W - U$ correlations are close to being "single-order-parameter liquids" in the classical Prigogine-Defay sense [15]. This implies that complex frequency-dependent thermoviscoelastic response functions like the isobaric/isochoric dynamic specific heat, dynamic thermal expansion coefficient, dynamic compressibility, etc, are all given by a single function [14]. In particular, these cannot "decouple" [16] from one another – they must all exhibit relaxations in the same frequency range. It has also been shown that strongly correlating viscous liquids obey density scaling, i.e., that if the relaxation time τ is measured at different temperatures and density ρ , τ is a unique function

of ρ^x/T [17]. Moreover, the exponent x may be determined from studies of $W - U$ correlations at a single state point [18]. Finally, it was recently found that strongly correlating viscous liquids have much simpler ageing properties than do viscous liquids in general (unpublished).

Fluctuations are ensemble dependent, of course, and one may ask what happens if fluctuations are instead studied in the ensemble of constant temperature and pressure (NpT ensemble). In this case virial fluctuations are not interesting, but in the NpT ensemble there are equally strong correlations for simple liquids between the fluctuations of volume and potential energy [7]. This is the ensemble used below for studying biomembrane thermodynamic fluctuations.

Based on the findings for simple model liquids and the Heimburg-Jackson theory we found it would be interesting to simulate phospholipid membranes in order to investigate whether the Heimburg-Jackson assumption of strong $V - U$ correlations is confirmed even for such complex systems. A phospholipid has both van der Waals interactions between its acyl chains and hydrogen bonds in the head region. Similarities to simple liquids are not at all obvious, and the microscopic origin of the enthalpy/volume correlations tentatively derived from experiments [5, 6] is not trivial.

Because of the large amount of water in the system one does not expect strong instantaneous correlations of phospholipid membrane thermodynamic fluctuations. The Heimburg-Jackson theory, however, in reality only relates to strong correlations of the biomembrane's slow degrees of freedom (on millisecond time scales), and so do the experiments they quote indicating strong correlations [5, 6]. This is analogous to the situation for highly viscous liquids where time-scale separation between the fast, vibrational degrees of freedom and the much slower configurational is also essential.

Phospholipids are the major constituent of biological membranes. Close to physiological temperature membranes undergoes a transition from a disordered phase (L_α phase) to an ordered phase (L_β) [4, 19]. Below we evaluate the strength of $V - U$ correlations for both the disordered and ordered phases with main focus on the high-temperature disordered phase. The correlation strength was calculated on a range of time scales. We show that $V - U$ correlate strongly, but only on long time scales. We furthermore investigated how well membrane area as well as membrane order-parameter fluctuations correlate with V and U fluctuations; such correlations are generally poor. Finally, the cause of the correlations is identified by splitting volume as well as energy into contributions from tails, heads, and water: The slow, strongly correlating $V - U$ fluctuations are shown to derive from the tails that are dominated by van der Waals interactions, thus establishing a conceptual link to the strong correlations of the slow pressure-energy fluctuations – the virial/potential energy correlations – of simple van der Waals liquids [8].

Simulations details

Details of the seven membrane simulations performed are listed in Tabel 1. The following abbreviations are used: DMPC-f: a fully hydrated di-myristoyl-phosphatidyl-choline membrane in the fluid phase. DMPC-g: a fully hydrated di-myristoyl-phosphatidyl-cholin membrane in the ordered phase. DPPC-f: a fully hydrated di-palmitoyl-phosphatidyl-choline membrane in the fluid phase. DPPC-g: a fully hydrated di-palmitoyl-phosphatidyl-choline membrane the ordered phase. DPPG: a fully hydrated di-palmitoyl-phosphatidyl-glycerol membrane in the fluid phase with calcium counter ions. DPPS: a fully hydrated di-myristoyl-phosphatidyl-serine membrane in the fluid phase with calcium counter ions. DMPSH: a fully hydrated and protonated di-myristoyl-phosphatidyl-serine membrane in the fluid phase.

In all simulations a time step of 1.0 fs was used. Temperature and pressure were controlled by the Langevin thermostat (damping coefficient: 5 ps^{-1}) and Nose-Hoover Langevin barostat (anisotropic regulation; piston oscillation time: 100 fs; damping time: 50 fs) [11]. Electrostatic interactions were evaluated using the Particle-Mesh-Ewald method [20, 21] with a grid spacing $\sim 1 \text{ \AA}$ and were updated every 4 fs. Van der Waals interactions were cut-off at 12 \AA in combination with a switching function starting at 10 \AA . Periodic boundary conditions were applied in all three dimensions. Simulations were carried out using NAMD [22].

The simulations of DMPC-f, DPPC-f, DPPG, DPPS, DMPS and DMPSH started from configurations taken from Refs. [23, 24, 25]. Initial configurations of DMPC-g and DPPC-g were built from a membrane simulated by Venable and co-workers [26]. The acyl chains remain in an ordered structure (as shown on Fig. 1), and they are referred to as "ordered".

Thermal equilibrium was ensured by monitoring the membrane area; only trajectories with no drift (compared to the thermal fluctuations) were used in the data analysis. The length of the equilibrium trajectories is listed in Table 1 in the column under t_{prod} . The importance of equilibrium should be emphasized, since an apparent strong correlation would appear if volume and energy relax from some (arbitrary) out-of-equilibrium state.

Results

The following collective quantities were evaluated every 0.5 ps: Potential energy U , simulation box volume $V = XYZ$ (where X , Y and Z are the box dimensions), projected membrane area $A = XY$, box thickness Z , and average chain order parameter $\langle S_{CD} \rangle_{ch}$. The latter parameter, which characterizes the overall acyl-chain order [27], is defined as $\langle S_{CD} \rangle_{ch} = | \langle \frac{3}{2} \cos^2(\theta_{CD}) - \frac{1}{2} \rangle_{ch} |$ where θ_{CD} is the angle between the membrane normal and (\vec{z}) the C-H bond of a given methylene group, and $\langle \dots \rangle_{ch}$ denotes an average over all methylene groups in all chains.

First, we consider the fluid DMPC-f membrane. The instantaneous fluctu-

Table 1: Overview of simulations details and results

(A) System abv. (phase)	t_{sim} [ns]	t_{prod} [ns]	N_{lip}	T [K]	N_{wat}/N_{lip}
DMPC-f (fluid)	151	121	128	330	33
DMPC-g (ordered)	65	36	64	286	33
DPPC-f (fluid)	180	124	72	325	29
DPPC-g (ordered)	78	48	64	304	33
DMPG (fluid)	149	49	128	330	33
DMPS (fluid)	139	49	128	340	36
DMPH (fluid)	136	35	128	340	37

(B) System abv. (phase)	$R_{\bar{U}\bar{V}}$	γ	$R_{\bar{U}\bar{U}_t}$	$R_{\bar{U}\bar{A}}$	$R_{\bar{V}\bar{A}}$	$R_{\bar{A}\bar{S}_{CD}}$	$R_{\bar{U}\bar{S}_{CD}}$	$R_{\bar{V}\bar{S}_{CD}}$
DMPC-f (fluid)	0.77	6.7	0.82	0.50	0.57	-0.75	-0.49	-0.54
DMPC-g (ordered)	0.47	4.3	0.31	0.02	0.05	-0.64	0.12	0.14
DPPC-f (fluid)	0.87	7.1	0.89	-0.29	-0.36	0.00	-0.61	-0.71
DPPC-g (ordered)	0.75	4.6	0.71	-0.16	0.12	-0.67	0.09	-0.07
DMPG (fluid)	0.82	5.9	0.80	0.41	0.40	-0.76	0.01	0.08
DMPS (fluid)	0.59	5.3	0.64	0.30	0.28	-0.71	0.04	0.20
DMPH (fluid)	0.78	9.2	0.84	0.43	0.51	-0.50	0.05	0.14

(A) t_{sim} : Total simulation time in nanoseconds. t_{prod} : Length of production run in nanoseconds (only membranes in quasi-equilibrium, i.e., with no detectable drift in the area per molecule, were included in the data analysis); N_{lip} : Number of lipid molecules; T : Temperature in Kelvin; N_{wat}/N_{lip} : Number of water molecules per lipid molecule. (B) $R_{\bar{U}\bar{V}}$: Energy-Volume correlation coefficient (see Eq. 1); γ : Energy-volume scaling factor in $\text{\AA}^3 \text{ mol/kcal}$ (see Eq. 13); $R_{\bar{U}\bar{U}_t}$: Energy-“Energy of acyl groups” correlation coefficient. $R_{\bar{U}\bar{A}}$: Energy-Area correlation coefficient; $R_{\bar{V}\bar{A}}$: Volume-Area correlation coefficient. $R_{\bar{A}\bar{S}_{CD}}$: Area-“chain order-parameter” correlation coefficient; $R_{\bar{U}\bar{S}_{CD}}$: Energy-“chain order-parameter” correlation coefficient; $R_{\bar{V}\bar{S}_{CD}}$: Volume-“chain order-parameter” correlation coefficient.

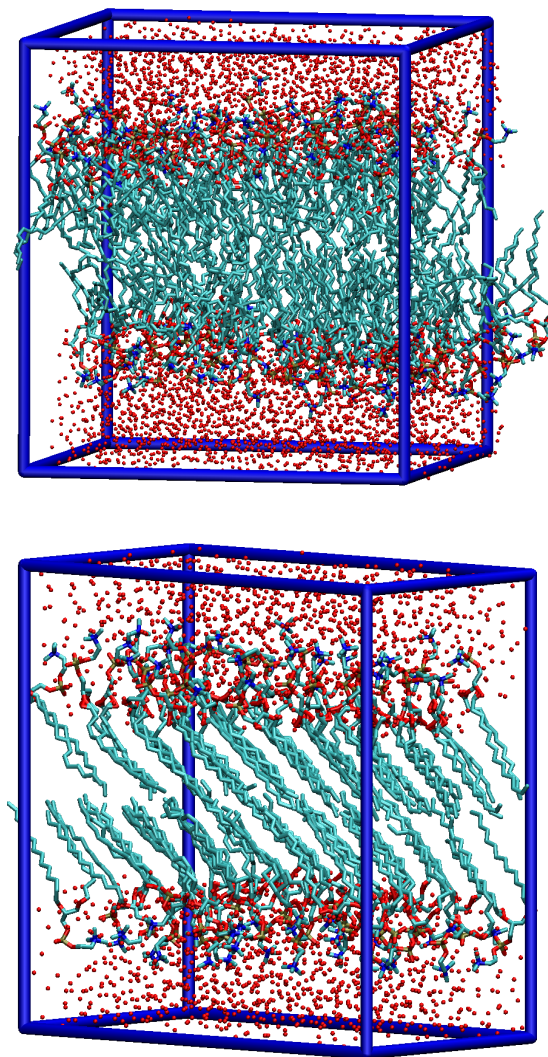


Figure 1: Snapshots of DMPC membrane in the fluid phase (DMPC-f; top) and in the ordered phase (DMPC-g; bottom). The red atoms are the oxygen atoms of water molecules; hydrogen atoms were removed for visual clarity (but included in the simulations). The green strings are the acyl chains. The frame indicates the periodic boundary box.

ations of volume and energy do not show any significant correlation (data not shown). This is not surprising, since a significant part of the simulation box is water and water is known not to have such correlation [8]. However, if fluctuations are averaged over time windows of 0.5 nanosecond, volume and energy are strongly correlated as shown in Fig. 2A for DMPC-f. This is quantified by the correlation coefficient,

$$R_{UV} = \frac{\langle \Delta \bar{U} \Delta \bar{V} \rangle}{\sqrt{\langle (\Delta \bar{U})^2 \rangle \langle (\Delta \bar{V})^2 \rangle}} = 0.77, \quad (1)$$

where the bar here and henceforth indicates a 0.5 ns average. $R = 0$ corresponds to no correlation, $|R| \cong 1$ corresponds to strong correlation. For comparison the correlation coefficient without averaging (R_{UV}) is 0.35.

One possible explanation for the observed strong correlation could be that the order of the acyl chains is the single controlling parameter of the fluctuations. If chains, as a result of a thermal fluctuation, become more ordered, one expects: decrease of energy, volume, and area, but increase of thickness and $\langle S_{CD} \rangle_{ch}$. We find $R_{\bar{U}\bar{A}} = 0.50$ and $R_{\bar{V}\bar{A}} = 0.57$. The correlation has the right sign but is significantly lower. The same is the case for Z and $\langle S_{CD} \rangle_{ch}$. Fig. 2B shows the full correlation matrix. Clearly a single parameter description is not sufficient. We need two parameters to describe the thermodynamic fluctuations: one parameter controlling V and U and one “geometrical” parameter controlling A , Z , and $\langle S_{CD} \rangle_{ch}$.

Table 1 shows that the DMPC-f, DPPC-g, DPPC-g, DMPG, DMPS, and DMPSH have strong volume-energy correlation ($R \geq 0.75$). The volumes DMPC-g and DMPS show less correlation with energy – a point returned to below.

The term “slow fluctuations” has so far been arbitrary, defined via the 0.5 ns averaging time window. A more general approach is to investigate the time-dependent correlation coefficient

$$\Gamma_{UV}(t) = \frac{\langle \Delta U(0) \Delta V(t) \rangle}{\sqrt{\langle \Delta U(0) \Delta U(t) \rangle \langle \Delta V(0) \Delta V(t) \rangle}}. \quad (2)$$

Similarly, one defines the time-dependent energy-area correlation coefficient $\Gamma_{UA}(t)$.

Fig. 3 shows $\Gamma_{UV}(t)$ and $\Gamma_{UA}(t)$ for all seven investigated system. In contrast to $\Gamma_{UA}(t)$ we observe strong correlation on slow time scales for $\Gamma_{UV}(t)$ where this function approaches unity. In the next section the slow parts of the volume and energy fluctuations are investigated via the autocorrelation functions $\langle \Delta V(0) \Delta V(t) \rangle$ and $\langle \Delta U(0) \Delta U(t) \rangle$.

Locating the slow volume and energy fluctuations

A membrane is a highly anisotropic system, and it is reasonable to divide it into regions. In the following three regions are defined: t , h , and w , where t (tail) refers to the hydrophobic acyl-chain atoms (i.e., atoms of methylene- and

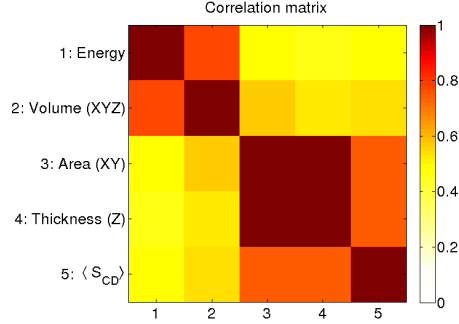
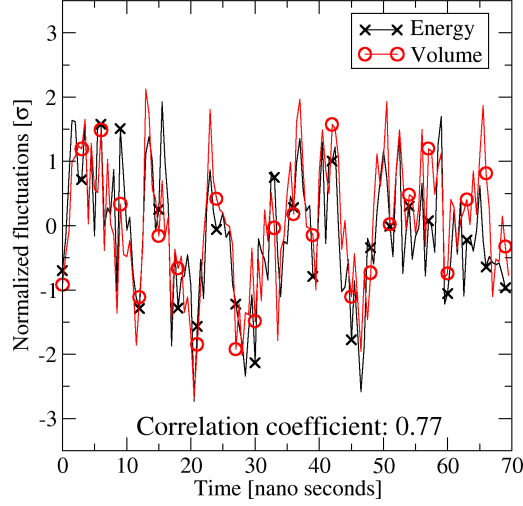


Figure 2: Correlations in the slow thermal equilibrium fluctuations of volume and energy (top) and correlation matrix for the DMPC-f membrane (bottom). The normalized fluctuations of volume and potential energy shown are averaged over time intervals of 0.5 nanosecond. Data are shifted and scaled such that the average value is zero and the standard deviation is unity. A significant correlations is observed quantified by the correlation coefficient, $R_{\bar{U}\bar{V}} = 0.77$ (this strong correlations can be associated to the acyl chains as seen by the similarities between this figure and the below Fig 5). The bottom panel represents the absolute values of the elements of the correlation matrix of energy, volume, membrane area, thickness and the average chain order-parameter where dark red illustrates strong correlation. Membrane area, thickness, and average chain order-parameter are strongly correlated, but these quantities only correlate weakly with energy and volume. Similar results are found for the other fluid membranes (except for DMPC-g and DMPS where the energy-volume correlation is only 0.47 and 0.59, respectively), see Table 1.

methyl groups in the acyl-chain), h (head) refers to the hydrophilic atoms (the remaining of the lipid atoms), and w refers to the water atoms.

To identify the origin of the slow volume fluctuations, we construct Voronoi polyhedra [28] of heavy atoms (i.e., ignoring hydrogen) and sum the Voronoi volumes for the regions t , h and w . In this way the total volume of the simulation box is divided into three terms,

$$V = V_t + V_h + V_w. \quad (3)$$

The auto-correlation function of the volume in Eq. 2 can now be split into a sum of three auto- and three cross-correlation functions,

$$\begin{aligned} \langle \Delta V(0) \Delta V(t) \rangle &= \langle \Delta V_t(0) \Delta V_t(t) \rangle \\ &+ \langle \Delta V_h(0) \Delta V_h(t) \rangle \\ &+ \langle \Delta V_w(0) \Delta V_w(t) \rangle \\ &+ 2 \langle \Delta V_t(0) \Delta V_h(t) \rangle \\ &+ 2 \langle \Delta V_t(0) \Delta V_w(t) \rangle \\ &+ 2 \langle \Delta V_h(0) \Delta V_w(t) \rangle. \end{aligned} \quad (4)$$

Fig. 4A shows these six functions for the DMPC-f membrane. The only nonvanishing function at long times (responsible for the slow fluctuations) is the auto-correlation function of the hydrophobic (tail) part of the membrane, $\langle \Delta V_t(0) \Delta V_t(0) \rangle$. This is quantified by $R_{\bar{V}\bar{V}_t} = 0.94$ being close to unity.

In the simulation, the potential energy of the system consists of a sum of Lennard-Jones terms, Coulomb pair energy terms, and intramolecular binding-energies:

$$U = U^{\text{intra}} + \frac{1}{2} \sum_i \sum_{j \neq i} U_{ij}^{\text{coul}} + \frac{1}{2} \sum_i \sum_{j \neq i} U_{ij}^{\text{LJ}}. \quad (5)$$

Again we split the total potential energy into contributions from regions of tails, heads and water,

$$U = U_t + U_h + U_w \quad (6)$$

where

$$U_x = U_x^{\text{intra}} + \frac{1}{2} \sum_{i=x} \sum_{j=\text{all}} U_{ij}^{\text{coul}} + \frac{1}{2} \sum_{i=x} \sum_{j=\text{all}} U_{ij}^{\text{LJ}}, \quad (7)$$

with x either tail, head, or water,

$$U_{ij}^{\text{LJ}} = 4\epsilon_{ij}((\sigma_{ij}/r_{ij})^{12} - (\sigma_{ij}/r_{ij})^6), \quad (8)$$

and

$$U_{ij}^{\text{coul}} = q_i q_j / (4\pi\epsilon_0 r_{ij}). \quad (9)$$

As for the volume, the auto-correlation function of the energy fluctuations in Eq. 2 is also split into a sum of three auto- and three cross correlation functions,

$$\begin{aligned}
\langle \Delta U(0) \Delta U(t) \rangle &= \langle \Delta U_t(0) \Delta U_t(t) \rangle \\
&+ \langle \Delta U_h(0) \Delta U_h(t) \rangle \\
&+ \langle \Delta U_w(0) \Delta U_w(t) \rangle \\
&+ 2\langle \Delta U_t(0) \Delta U_h(t) \rangle \\
&+ 2\langle \Delta U_t(0) \Delta U_w(t) \rangle \\
&+ 2\langle \Delta U_h(0) \Delta U_w(t) \rangle.
\end{aligned} \tag{10}$$

Fig. 4B shows the six auto- and cross correlation functions of U_t , U_h and U_w . Again, the slow fluctuations are dominated by the tail region. It should be noted, though, that the head-head and water-water auto-correlation remaining functions are not close to vanishing, as was the case for the volume fluctuations. This is quantified by $R_{\bar{U}\bar{U}_t} = 0.82$ (Tabel 1) not being as close to unity as $R_{\bar{V}\bar{V}_t} = 0.94$.

Fig. 4C shows the auto- and cross-correlation functions corresponding to a further splitting of the tail energy into “intramolecular interactions”, “Coulombic interactions” and “van der Waals interactions” given in Eq. 7. The van der Waals energies dominate the energy fluctuations of the tail region.

The above analysis shows that the slow energy-volume correlation originate from van der Walls interactions in the tail region; thus:

$$\Delta \bar{V}_t \propto \Delta \bar{U}_t^{LJ}, \tag{11}$$

where

$$U_t^{LJ} = \frac{1}{2} \sum_{i=\text{tails}} \sum_{j=\text{all}} U_{ij}^{LJ} \tag{12}$$

This is in good agreement with the findings for simple strongly correlations liquids [9, 10]. It should be remembered, however, that we discarded some non-vanishing energy correlation functions. If we correlate the slow fluctuations (by doing a 0.5 ns average) of the Voronoi volume of the acyl chains and the van der Waals energy of tails, we find a correlation coefficient of $R_{\bar{V}_t \bar{U}_t^{LJ}} = 0.87$ (Fig. 5). The same number for the fluctuations for whole simulation box was $R_{\bar{V}\bar{U}} = 0.77$. The loss of correlation is associated with the energy terms neglected. Consistent with this, Table 1 shows a general correlation between $R_{\bar{V}\bar{U}}$ and $R_{\bar{U}\bar{U}_t}$.

It is convenient to define a volume-energy scaling factor via

$$\gamma = \sqrt{\frac{\langle (\Delta V)^2 \rangle}{\langle (\Delta U)^2 \rangle}}. \tag{13}$$

For DMPC the experimentally found volume-energy scaling factor, $\gamma = (7.788 \pm 0.110) \times 10^{-4} \text{ mL/J} = (5.418 \pm 0.077) \text{ \AA} \cdot \text{mol/kcal}$ [6], is in good agreement with the scaling factors given in Table 1.

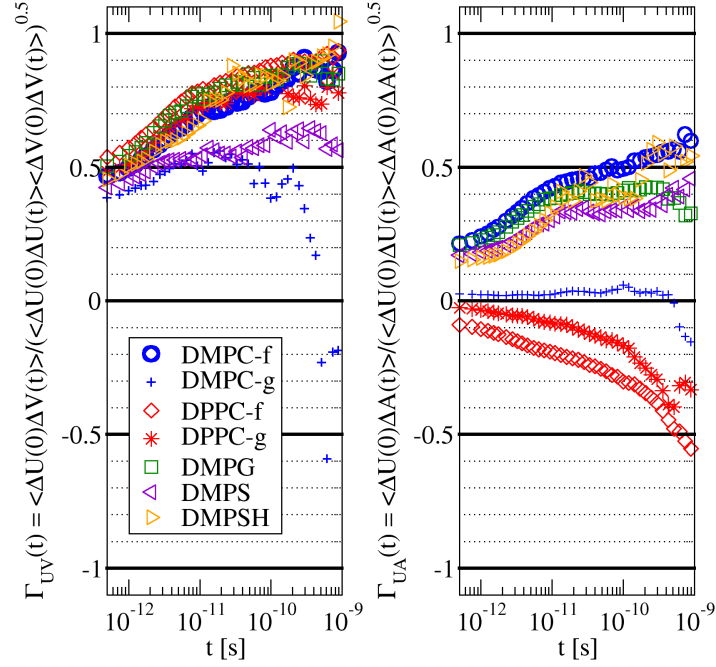


Figure 3: Time-dependent correlation coefficient $\Gamma(t)$ of volume-energy (left) and area-energy (right) of membranes in the fluid phase (the definition of $\Gamma(t)$ is given on the y-axis). The fast fluctuations of volume and energy, e.g. $t < 10^{-11}$ second, correlate only weakly, whereas the slow fluctuations, e.g. $t \simeq 10^{-9}$ second, are strongly correlated. The area and energy fluctuations are only weakly correlated.

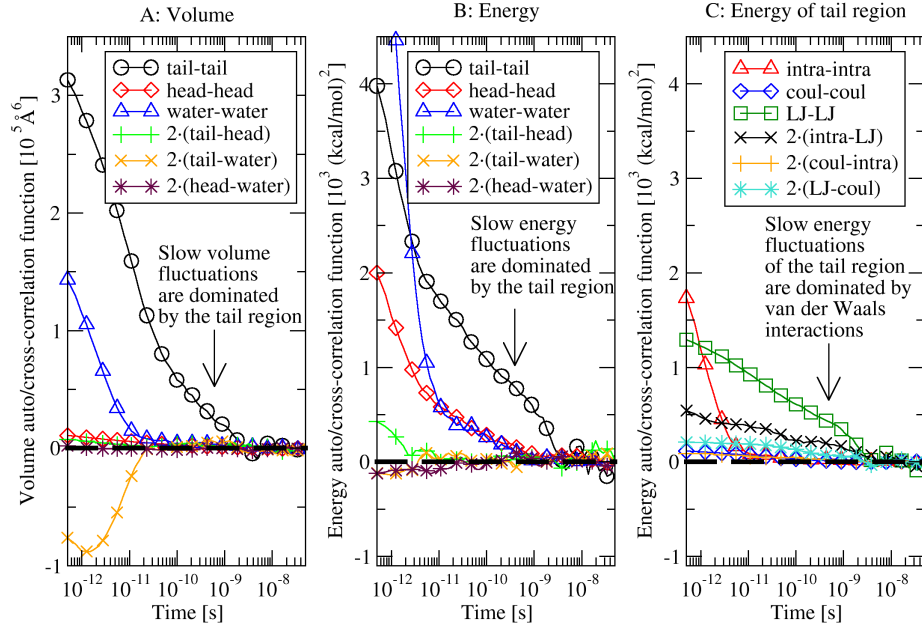


Figure 4: Six auto- and cross-correlations for the DMPC-f membrane. Panel A: Volume correlations of the three regions (Eq. 4): tails (methylene and methyl groups), heads, and water. From these correlations it can be concluded that the slow volume fluctuations are dominated by the acyl chains. Panel B: Energies of the three regions (Eq. 10). Again, slow fluctuations are dominated by the tail region. Panel C: Energy correlations split into intramolecular, Lennard-Jones (LJ) and Coulombic energies (Eq. 6).

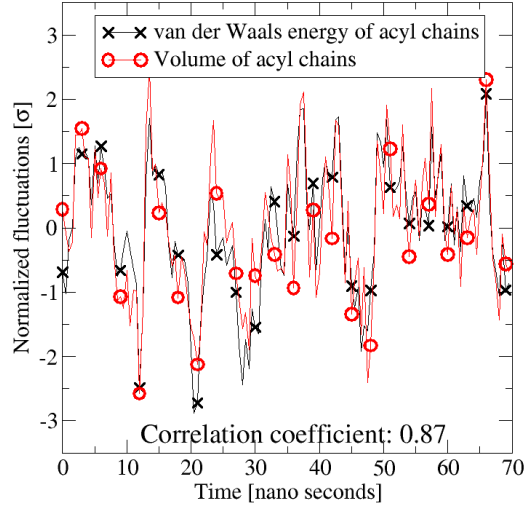


Figure 5: Normalized fluctuations of Voronoi volume and van der Waals energy of the acyl chains of the DMPC-f membrane. Data are shifted and scaled so the average value is zero and the standard deviation is unity. The correlation is strong with a correlation coefficient of 0.87. Note the similarity to Fig. 2A.

Conclusions

This paper reports a study of biomembranes’ thermodynamic equilibrium fluctuations. On the long time scale we identify strong volume-energy correlations of a kind that were previously only observed for simple model liquids [7, 8]. These correlations are mainly documented in the fluid phase, but we also show that they exist in the membrane’s gel phase.

It may seem surprising that a complex system like a biomembrane exhibits such strong thermodynamic correlations. The identification of the origin of the correlations as deriving from the van der Waals interactions of the hydrophobic part of the membrane, however, points to a common origin of strong thermodynamic correlations in simple van der Waals liquids and biomembranes. This is consistent with the finding that there are strong energy-volume correlations in both fluid and gel phases: The correlations do not depend on the degree of chain order, as for simple liquids where the strong correlations survive crystallization [9, 10].

Regarding the Heimburg-Jackson nerve signal theory, our findings largely confirm the assumption of this theory that volume and energy (enthalpy) correlate for microstates. We find a strong correlation only on the nanosecond and longer time scales, which are however the relevant times for nerve signals. One caveat is that, although we do find strong energy-volume correlations in both the fluid and gel phases, the proportionality constant γ is not the same in both phases (Table 1). This shows that the nature of the correlations changes when passing the phase transition, in contrast to our findings for crystallization of the standard Lennard-Jones liquid [9, 10]. More work is needed to clarify the cause of this difference between biomembranes and simple liquids.

Acknowledgments

The authors wish to thank Richard M. Venable for providing a configuration of an ordered membrane. The centre for viscous liquid dynamics “Glass and Time” and MEMPHYS are both sponsored by the Danish National Research Foundation. Simulations were performed at the Danish Center for Scientific Computing at the University of Southern Denmark.

References

- [1] Heimburg T, Jackson AD (2005) On soliton propagation in biomembranes and nerves. *PNAS* 102:9790-9795.
- [2] Heimburg T, Jackson AD (2007) The thermodynamics of general anesthesia. *Biophys. J.* 92:3159-3165.
- [3] Hodgkin, AL, Huxley, AF (1952) A quantitative description of membrane current and its applications to conducting and excitation in nerve. *J. Physiol. (London)* 117:500-544.

- [4] Nielsen LK, Bjørnholm T, Mouritsen OG (2007) Thermodynamic and real-space structural evidence of a 2D critical point in phospholipid monolayers. *Langmuir* 23:11684-11692.
- [5] Heimburg, T (1998) Mechanical aspects of membrane thermodynamics. Estimation of the mechanical properties of lipid membranes close to the chain melting transition from calorimetry. *Biochim. Biophys. Acta* 1415:147-162.
- [6] Ebel H, Grabitz P, Heimburg, T (2001) Enthalpy and volume changes in lipid membranes. I. The proportionality of heat and volume changes in the lipid melting transition and its implication for the elastic constants. *J. Phys. Chem. B* 105:7353-7360.
- [7] Pedersen UR, Christensen T, Schrøder TB, Dyre JC (2008) Feasibility of a single-parameter description of equilibrium viscous liquid dynamics. *Phys. Rev. E* 77:011201.
- [8] Pedersen UR, Bailey NP, Schrøder TB, Dyre JC (2008) Strong pressure-energy correlations in van der waals liquids. *Phys Rev. Lett.* 100:015701.
- [9] Bailey NP, Pedersen UR, Gnan N, Schrøder TB, Dyre JC (2008) Pressure-energy correlations in liquids. I. Results from computer simulations. *J. Chem. Phys.*, in press.
- [10] Bailey NP, Pedersen UR, Gnan N, Schrøder TB, Dyre JC (2008) Pressure-energy correlations in liquids. II. Analysis and consequences. *J. Chem. Phys.*, in press.
- [11] Feller SE, Zhang YH, Pastor RW and Brooks BR (1995) Constant pressure molecular dynamics simulations: the Langevin piston method. *J. Chem. Phys* 103:4613-4621
- [12] Allen MP, Tildesley DJ (1989) *Computer simulation of liquids* (Oxford University Press).
- [13] Kob W, Andersen HC (1994) Scaling behavior in the beta-relaxation regime of a supercooled Lennard-Jones mixture. *Phys. Rev. Lett.* 73:1376-1379.
- [14] Ellegaard NL, *et al.* (2007) Single-order-parameter description of glass-forming liquids: A one-frequency test. *J. Chem. Phys.* 126:074502.
- [15] Davies RO, Jones GO (1952) The irreversible approach to equilibrium in glasses. *Proc. Roy. Soc. A (London)* 217:26-42.
- [16] Angell CA (1991) Relaxation in liquids, polymers and plastic crystals - strong fragile patterns and problems. *J. Non-Cryst. Solids* 131:13-31.
- [17] Roland CM, Hensel-Bielowka S, Paluch M, Casalini R (2005) Supercooled dynamics of glass-forming liquids and polymers under hydrostatic pressure. *Rep. Prog. Phys.* 68:1405-1478.

- [18] Schröder TB, Pedersen UR, Dyre JC (2008) Density scaling as a property of strongly correlating viscous liquids. *arXiv.org* arXiv:0803.2199.
- [19] Zhang R, *et al.*, (1995) Critical Fluctuations of Membranes. *Phys. Rev.* 74:2832-2835.
- [20] Darden T, York D, Pedersen L (1993) Particle mesh ewald: an $N \cdot \log(N)$ methods for Ewald sums in large systems. *J. Chem. Phys.* 98:10089-10092.
- [21] Essmann U, *et al.* (1995) A smooth particle mesh Ewald method. *J. Chem. Phys.* 103:8577-8593.
- [22] Kale L, *et al.* (1999) NAMD2: Greater Scalability for Parallel Molecular Dynamics. *J. Comput. Phys.* 151:283-312.
- [23] Pedersen UR, Leidy C, Westh P, Peters GH (2006) The effect of calcium on the properties of charged phospholipid bilayers. *Biochim. Biophys. Acta, Biomembr.* 1758:573-582.
- [24] Pedersen UR, Peters GH, Westh P (2007) Molecular packing in 1-hexanol-DMPC bilayers studied by molecular dynamics simulation. *Biophysical Chemistry* 125, 104-111.
- [25] Sonne J, Jensen MØ, Hansen FY, Hemmingsen L, Peters GH (2007) Reparameterization of all-atom dipalmitoylphosphatidylcholine lipid parameters enables simulations of fluid bilayers at zero tension. *Biophys. J.* 92:4157-4167.
- [26] Venable RM, Brooks B., Pastor RW (2000) Molecular dynamics simulations of gel (L-beta I) phase lipid bilayers in constant pressure and constant surface area ensembles. *J. Chem. Phys.* 112, 4822-4832.
- [27] Tieleman DP, Berendsen HJC (1996) Molecular dynamics simulations of a fully hydrated dipalmitoyl phosphatidylcholine bilayer with different macroscopic boundary conditions and parameters. *J. Chem. Phys.* 105:4871-4880.
- [28] Voronoi G (1908) New parametric applications concerning the theory of quadratic forms - Second announcement. *J. Reine Angew. Math.* 134:198-287.